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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on March 13, 1992 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☐ Claims 1-48 are pending in the applicatio
   Of the above, claims 2-8, 9-11, 16-25, 29-36, +40-46 are withdrawn from consideratio
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 12-15, 26-28, 37-39, +47-48 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-48 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1, 12-15, 26-28, 37-39, and 47-48, drawn to proteins, particles, and vaccines, classified in Class 530, subclass 350 and Class 424, subclass 88.

II. Claims 2-8, 16-22, 29-33, and 40-44, drawn to DNA, transformed host cells, and a method of making or expressing the protein, classified in Class 435, subclass 69.3.

III. Claims 9-11, 23-25, 34-36, and 45-46, drawn to a measuring or testing process, classified in Class 435, subclass 7.1.

Inventions II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the product as claimed can be made by another materially different process such as the Merrifield chemical synthesis technique.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a

materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product as claimed can be used for a different process such as eliciting an immune response as a vaccine.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

During a telephone conversation with Thomas Moran on November 24, 1992 a provisional election was made with traverse to prosecute the invention of proteins, particles, and vaccines, in claims 1, 12-15, 26-28, 37-39, and 47-48 . Affirmation of this election must be made by applicant in responding to this Office action. Claims 2-11, 16-25, 29-36, and 40-46 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 12, 13, 26, 27, 37, 38, 47, and 48 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

The specification has failed to provide evidence of a patentable utility for the vaccines of claims 12-13, 26-27, 37-38, and 47-48. The art recognized definition of a vaccine encompasses the ability of the immunogen to elicit protective immunity to a secondary challenge. The applicant has not provided substantive evidence that the claimed vaccines are immunogenic and elicit protective immunity in human subjects or an appropriate animal model. The recognition of the instant proteins by human sera from infected donors is not indicative of the ability to elicit a protective immune response by administration of the instant proteins.

It is well established that a patent may not be granted on a chemical compound unless a utility is shown, other than that for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification fails to teach the use of the claimed recombinant proteins and particles as a vaccine as in claims 12-13, 26-27, 37-38, and 47-48. Specifically, the specification fails to provide information such as the method of administration, the appropriate amount to administer, a effective vaccination schedule that elicits long-term protective immunity, what adjuvants are to be utilized, etc. Accordingly, the specification fails to provide an enabling disclosure for one of ordinary skill in the art to effectively use the claimed vaccines.

Similarly, the specification fails to provide evidence of an effective adjuvant to be used with the vaccines as in claims 12, 26, 37, and 47. As the specification lacks information as to whether the claimed vaccines effectively elicit protective immunity, it would take undue experimentation for one of ordinary

skill in the art to select an effective adjuvant to be utilized in the claimed vaccines.

The specification fails to teach the production of vaccines containing an "antigenically active" portion of VP1 or VP2 as in claims 12, and 26. The specification fails to describe the construction of baculovirus vectors containing an antigenically active portion of VP1 or VP2. Furthermore, the specification fails to provide information as to what portions of VP1 and VP2 are antigenically active. Therefore, in light of the limited teachings of the specification, and the lack of data indicating what portions of VP1 and VP2 are epitopes that elicit neutralizing antibodies, it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed.

The specification teaches only the expression and subsequent particle formation of VP2. The specification fails to teach the formation of particles consisting of VP1 and VP2 as in claim 28. It is not clear that particles were formed from the co-expression of VP1 and VP2 in insect cells infected with the recombinant viruses. Therefore, in light of the limited teachings of the specification, it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed. See Ex Parte Forman, 230 USPQ 546.

The specification fails to teach the construction of recombinant baculovirus vectors containing epitopes of proteins

of other pathogens incorporated into the coding sequence for VP2, the expression of such proteins, and the subsequent particle formation as in claim 39. The specification provides no information as to where the fusions would be made within VP2, whether the fusion protein would still form particles, or whether the fused epitope from another pathogen would be effectively presented at the surface of the recombinant particle. Therefore, in light of the limited teachings of the specification it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed.

Claims 12-13, 26-28, 37-39, and 47-48 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 12, 26, 37, and 47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 26 are vague and indefinite in the recitation of "antigenically active portion". The meaning of antigenically active is unclear. Furthermore, it is not clear what fragment or portion of the protein applicant is referring to.

Claims 12, 26, 37, and 47 are vague and indefinite in the recitation of "carrier". It is not clear what carrier applicant is referring to.

Claims 13, 27, and 48 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. The recitation of a specific use for a product does not further limit the previous claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ozawa et al (J. Virol. 61(8):2627-2630).

Ozawa et al disclose the B19 parvovirus capsid proteins generated in bone marrow mononuclear cells. Figure 1 shows the detection of the immunoprecipitated non-fused capsid proteins VP2 and VP1 that have molecular weights of 58 and 84 Kd, respectively. As it is not clear that there is any functional difference between the instant proteins and the proteins produced by Ozawa et al, and it is not clear if the instant proteins are in an isolated and purified form, the applicants claims are fully met by this reference.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1, 12, and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Sisk et al, and Cotmore et al in view of Smith et al, Pennock et al, Luckow et al and Wood et al.

If the applicant has support for the capsid protein VP1 being in isolated form, claims 1, 12, and 13 are unpatentable over the above references. Ozawa et al (J. Virol 61(8):2395-2406) disclose the transcription map of the B19 human parvovirus, including the location of the genes for the 84 Kd VP1 antigen and the 58 Kd VP2 antigen (p. 2403, Fig.9). Cotmore et al also disclose the location of the VP1 and VP2 genes on the human parvovirus B19 genome by shotgun cloning restriction fragments from the cloned viral genome, expressing those fragments in E. coli, and detecting the expressed capsid polypeptides with diagnostic human anti-B19 serum. See Fig.4 for the location of

the clone (pYT106) that expressed VP1 and VP2. Sisk et al disclose the expression of a VP1-β galactosidase fusion protein in E. coli that is recognized by anti-B19 serum. See Fig.4 and the first sentence of the discussion. Additionally, Sisk et al disclose the need to produce B19 viral capsid proteins by recombinant means as viral growth in tissue culture does not produce significant quantities of antigen (see Sisk et al, p. 1077, second paragraph). None of these references disclose the expression of VP1 or VP2 in recombinant baculovirus infected insect cells.

Wood et al disclose the expression of the VP-2 capsid protein from the related canine parvovirus from a recombinant baculovirus in insect cells. This protein was successfully utilized as a vaccine in dogs (see column 6).

Smith et al, Pennock et al, and Wood et al disclose the expression of heterologous proteins in infected insect cells using baculovirus as the vector. Smith et al recite on page 2164:

> "...Baculoviruses should prove to be important vectors for the production of cloned gene products in insect cells or organisms. The invertebrate cell will provide a unique biochemical environment for the production of foreign products and will complement vertebrate and prokaryotic host-vector systems. Potentially, any gene could be linked to the polyhedrin promoter, incorporated into the AcNPV

genome, and efficiently expressed in infected cells."

Smith et al also disclose on page 2156 that in infected cells, AcNPV polyhedrin accumulates to high levels and constitutes 25% or more of the total protein mass in the cell, and is probably synthesized in greater abundance than any other protein in a virus infected eukaryotic cell.

See also page 404 of Pennock et al, where the attractive features of the AcNPV are described:

> "(i) a capacity to accommodate large passenger DNA inserts in its expandable nucleocapsids, (ii) a strong promoter which allows for high level expression of fused passenger genes... Finally, baculoviruses have an additional level of biological safety which few other viruses have. They are known to infect only invertebrate, and the mechanism of organismal transfer primarily involves the occluded form of the virus."

Luckow et al further review the advantages of expressing heterologous proteins in the baculovirus-insect cell system. Luckow et al state that "recombinant proteins produces in insect cells with baculovirus vectors are biologically active and for the most part appear to undergo post-translational processing to produce recombinant products very similar to that of authentic proteins". See under Biological Activity of Recombinant Proteins. Table 1 also discloses the successful expression of 35

foreign genes by baculovirus vectors, including many viral capsid or envelope antigens.

Given the art recognized need for the large scale production of the human parvovirus B19 capsid antigens as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as exemplified by Ozawa et al (J. Virol 61(8):2395-2406) and Cotmore et al, as well as the disclosed expression in E. coli of the B19 capsid protein, it would have been obvious to one of ordinary skill in the art to express the VP1 coding sequence in a recombinant host cell for the large scale production of capsid antigen. Furthermore, given the advantages of utilizing the commercially available baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, as well as the previously disclosed use of the baculovirus expression system to produce a vaccine consisting of the canine parvovirus VP2 antigen, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to clone the coding sequence for VP1 into a baculovirus expression vector to produce large quantities of capsid antigen and suggest its use as a vaccine composition. It is obvious to employ known materials (genes and expression vectors) for their known and expected uses.

Claims 14, 26, and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Cotmore et al, and Sisk et al in view of Smith et al, Pennock et

al, Luckow et al and Wood et al.

If the applicant has support for the capsid protein VP2 being in isolated form, claims 14, 26, and 27 are unpatentable over the above references. As described above, Ozawa et al, Cotmore et al, and Sisk et al disclose the transcriptional patterns and thus the location of the VP2 coding sequence in the genome of human parvovirus B19 as well as the expression of the capsid protein in E. coli. Similarly, Smith et al, Pennock et al, and Luckow et al disclose the advantages of utilizing the baculovirus-insect cell expression system to produce large quantities of recombinant proteins. As described above, Wood et al disclose the production of a vaccine consisting of the canine parvovirus VP2 capsid protein using the baculovirus-insect cell expression system.

Given the art recognized need for the large scale production of the human parvovirus B19 capsid antigens as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as exemplified by Ozawa et al (J. Virol. 61(8):2395-2406), and Cotmore et al, as well as the disclosed expression in E. coli of the B19 capsid protein, it would have been obvious to one of ordinary skill in the art to express the VP2 coding sequence in a recombinant host cell for the large scale production of capsid antigen. Furthermore, given the advantages of utilizing the commercially available baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, as

well as the previously disclosed use of the baculovirus expression system to produce a vaccine consisting of the canine parvovirus VP2 capsid protein as exemplified by Wood et al, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to clone the coding sequence for VP2 into a baculovirus expression vector to produce large quantities of capsid antigen and suggest its use as a vaccine composition. It is obvious to employ known materials (genes and expression vectors) for their known and expected uses.

Claims 15, 28, 37, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Cotmore et al, Sisk et al, Smith et al, Pennock et al, Luckow et al, and Wood et al as applied to claim 14 above, and further in view of Kajigaya et al, Pintel et al, and Mazzara et al.

As described above the utilization of the baculovirus-insect cell expression system to produce large quantities of the human parvovirus B19 VP1 and VP2 capsid antigens would have been obvious to one of ordinary skill in the art. Pintel et al disclose the production of empty virion particles of the related parvovirus MVM in recombinant murine cells. The particles were produced from bovine pappilomavirus (BPV)-based vectors, in which were cloned the genome of MVM containing the VP1 and VP2 coding sequences. Kajigaya et al disclose the production of empty capsids of the B19 parvovirus from an engineered cell line that

contains the B19 VP1 and VP2 coding sequences. Mazzara et al disclose the production of empty canine parvovirus capsids in eukaryotic cells that express VP1 and VP2. Mazzara et al further suggest the extension of this technique to produce antigenic empty capsids made from the human parvovirus VP1 and VP2. See page 5.

Given the art recognized need to produce large quantities of the B19 capsid protein for diagnostic and potential vaccine use as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as described in Ozawa et al (J. Virol. 61(8):2395-2406) and Cotmore et al, the advantages of using the baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, and the previously disclosed production of a vaccine consisting of the canine parvovirus VP2 expressed in the baclovirus-insect cell expression system, it would have been obvious to express the genes for VP1 and VP2 in the baculovirus expression system. Furthermore, given the art recognized ability of parvovirus VP1 and VP2 to form empty virions in other expression systems as exemplified by Pintel et al, Kajigaya et al, and Mazzara et al, it would have been obvious, absent unexpected results, to produce empty virions consisting of VP2 or VP1 and VP2 in the baculovirus expression system and suggest their use in a vaccine composition.

Claims 39 and 47-48 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406),

Cotmore et al, Sisk et al, Smith et al, Pennock et al, Luckow et al, Wood et al, Kajigaya et al, Pintel et al, and Mazzara et al as applied to claim 15-28, and 37-38 above, and further in view of Evans et al, Borisova et al, and Clarke et al.

As set forth above, it would have been obvious to one of ordinary skill in the art to produce the claimed particles containing VP2 or VP1 and VP2 in the baculovirus expression system. Evans et al disclose the expression of an epitope of HIV-1 gp41 as a chimeric molecule inserted into the gene for the poliovirus capsid protein VP1. Clarke et al disclose the production of a vaccine consisting of an epitope from the capsid protein VP1 of the foot and mouth disease virus inserted into the coding sequence of HBcAg in E. coli. Borisova et al also disclose the use of the hepatitis B core antigen particles to express foreign antigens on the particle surface (HIV-1 gp41, and gp51 of bovine leukemia virus). See Table 1, p.123.

Given the art recognized need to produce large quantities of the B19 capsid protein for diagnostic and potential vaccine use as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as described in Ozawa et al (J. Virol. 61(8):2395-2406) and Cotmore et al, the advantages of using the baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, and the previously disclosed production of a vaccine consisting of the canine parvovirus VP2 expressed in the baclovirus-insect cell expression system, it

would have been obvious to express the genes for VP1 and VP2 in the baculovirus expression system. Furthermore, given the art recognized ability of parvovirus VP1 and VP2 to form empty virions in other expression systems as exemplified by Pintel et al, Kajigaya et al, and Mazzara et al, it would have been obvious, absent unexpected results, to produce empty virions consisting of VP2 or VP1 and VP2 in the baculovirus expression system. Additionally, given the art recognized utilization of human viral core or capsid proteins to express foreign antigens or epitopes of other pathogens, as exemplified by Evans et al, Clarke et al, and Borisova et al, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to insert the antigenic epitopes of other pathogens into the parvovirus VP2 coding sequence, express the chimeric gene in the baculovirus-insect cell expression system, and produce empty capsid particles expressing the foreign antigenic epitope on the particle surface.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael S. Tuscan whose telephone number is (703) 308-4240.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180

MST

Michael S. Tuscan Ph.D.
December 5, 1992